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13. ABSTRACT *(Maximum 200 Words)*

Purpose: Use the meta-analytic approach to examine the effects of exercise on bone mineral density (BMD) using individual patient data (IPD) and to compare these results with summary data from the same studies. **Scope:** The specific aim for this project period was to retrieve IPD from existing exercise training studies dealing with the effects of exercise on BMD. **Major findings:** Of the 76 eligible studies we were able to obtain IPD from 29 (38.2%). Binary multiple logistic regression analysis revealed a trend suggesting that authors of studies conducted in the United States were less likely to supply IPD when compared with authors who conducted studies in other countries (adjusted odds ratio = 0.324, 95% confidence interval = 0.104 to 1.004). Only 19.0% of authors from studies conducted in the United States versus 52.9% of authors from other countries provided us with IPD. **Results/Significance**: The results suggest moderate success in the acquisition of IPD for this data set. In addition, it appears that greater success can be obtained when IPD for this topic is requested from studies conducted in countries other than the United States.

14. SUBJECT TERMS
Exercise, bone, meta-analysis, osteoporosis, bine density, physical Activity, physical fitness, men ,women

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I. INTRODUCTION

Bone health is critical for optimal performance and the prevention of fractures associated with low bone mineral density (BMD). Our previous two years focused on using the meta-analytic approach to examine the effects of exercise on BMD in adult humans using summary means from completed studies. To date, no meta-analysis exists using individual patient data (IPD) to examine the effects of exercise on BMD. It is important to identify the feasibility of using IPD as well as whether results differ between summary and IPD. Thus, the purpose of this study is to extend our currently funded work, a meta-analysis of summary data, by including IPD and comparing it with the summary data. The specific aims of this project are to (1) compare summary versus IPD in relation to the overall magnitude of effect that exercise has on BMD, (2) compare summary versus IPD in relation to the effect of potentially confounding variables (age, training program, etc.) on changes in BMD, and (3) provide recommendations for future research regarding the use of summary versus IPD for examining the effects of exercise on BMD. The results of this project will help identify the best approach to use (summary versus IPD) when attempting to arrive at a more objective conclusion regarding the effects of exercise on BMD in humans. In addition, this will be the first meta-analysis using IPD in the area of exercise and BMD. Finally, the results of this project will provide the Armed Forces with a better understanding of the effects of exercise on BMD and will also help to identify what programs, if any, will provide for optimum bone development and maintenance.

II. BODY

A. Statement of Work

Our statement of work for the third year and whether the task was accomplished is listed in the table below.

Task	Time Line	Task Accomplished?
1. Search for addresses of authors to request data from	Year Three	Yes
2. Prepare and validate forms - Cover letter - Data request forms	Year Three	Yes
3. Mail data request forms to authors - Initial mailing - Follow-up mailing	Year Three	Yes
4. Coding - Modify coding sheet to handle individual patient data - Enter data retrieved	Year Three	Yes
5. Analyze data	Year Four	Pending
6. Prepare and present results at conferences	Year Four	Pending
7. Prepare manuscripts	Year Four	Pending

As can be seen, we have successfully completed all tasks as originally proposed in our statement of work. Despite the fact that we are in the third year of funding but only in the

first year of this phase of the project, we have already completed one study that is currently in review and of which the purpose was to examine the level of success for acquiring IPD for a meta-analysis on the effects of exercise on BMD in adults (See pages 8-23 of Appendices). Obtainment of IPD was derived from a database of 76 studies that was developed during the first year of this project and which met our previously defined inclusion criteria. During this phase of the project, a separate database with contact information for study authors was developed (See pages 24-26 of Appendices). Prior to requesting IPD from investigators, a cover letter and data request forms were developed, reviewed, revised, and finally approved by the Principal Investigator, Research Technician, and Consultant (See pages 22-23 of Appendices). Initial and follow-up request letters for IPD, separated by approximately five weeks, were then sent via postal-mail to the appropriate authors of the 76 studies. All authors who provided IPD were paid $40.00 (US) to help cover expenses. Of the 76 eligible studies we were able to obtain data from 29 (38.2%). Binary multiple logistic regression analysis revealed a trend suggesting that authors of studies conducted in the United States were less likely to supply IPD when compared with authors who conducted studies in other countries (adjusted odds ratio = 0.324, 95% confidence interval = 0.104 to 1.004). Only 19.0% of authors from studies conducted in the United States versus 52.9% of authors from other countries provided us with IPD. None of the other variables in our model (gender of author, source of publication, year of publication) were significant predictors for whether IPD were provided. We concluded that moderate success was obtained in the acquisition of IPD for a meta-analysis dealing with the effects of exercise training on bone mineral density in adults. We were more successful when IPD were requested from studies conducted in countries other than the United States.

In addition to the above-completed study, the Principal Investigator, Research Technician, and Consultant have developed, reviewed, revised, and finally approved a coding sheet for the coding of studies. Furthermore, the Principal Investigator and Research Technician coded all data from the 29 studies that supplied IPD. A total of 637,640 items were coded in computerized spreadsheet database (See pages 27-29 of Appendices for list of items coded).

III. KEY RESEARCH ACCOMPLISHMENTS

A. Identified that moderate success is obtained when attempting to retrieve IPD for studies dealing with the effects of exercise on BMD in adult humans.
B. Identified that the acquisition of IPD for exercise and BMD studies is more likely to occur if the study is conducted in a country other than the United States.

IV. REPORTABLE OUTCOMES

A. Manuscripts (Refereed)

1. Kelley, G.A., Kelley, K.S., Tran, Z.V. Retrieval of Individual Patient Data for an Exercise-Related Meta-Analysis (in review-See pages 8-23 of Appendices)

2. *Kelley, G.A., Kelley, K.S., Tran, Z.V. Resistance training and bone mineral density in women: A meta-analysis of controlled trials. American Journal of Physical Medicine and Rehabilitation 2001;80:65-77. (See pages 30-42 of Appendices)

3. **Kelley, G.A., Kelley, K.S., Tran, Z.V. Aerobic exercise and regional bone density in women: A meta-analysis of controlled trials. American Journal of Medicine & Sports (in press). (See pages 43-69 of Appendices)

   * Article is from our first two years of funding and was listed in our previous annual report as "in press" but is now published.

   ** Article is from our first two years of funding and was listed in our previous annual report as "in press" and is still "in press" but scheduled for publication in the November/December 2001 issue of the "The American Journal of Medicine & Sports."

B. Funding Applied For Based on Work Supported By This Award

1. We have not applied for any future funding because we are currently spending the next year focused on the analysis of data for this currently funded project.

V. CONCLUSIONS

A. Importance of Completed Research

Low BMD is a major public health problem. Unfortunately, the effects of exercise on BMD in adults are not well known. Given the large number of studies conducted and discrepant results, a meta-analysis was warranted. Our first two years of funding consisted of a meta-analysis of summary means from retrieved studies, with beneficial effects noted. However, a meta-analysis using IPD has the potential for increased statistical power as well as a more thorough examination of potential covariates. Consequently, this past year (third year) of funding as well as our next year of funding will focus on the use of IPD for examining the effects of exercise on BMD in adult humans. Our results to date suggest that moderate success can be obtained in the acquisition of IPD for a meta-analysis dealing with the effects of exercise training on BMD in adult humans. This research is important because it suggests that while meta-analysis of IPD has the potential for increased statistical power as well as a more thorough examination of potential covariates, this has to be countered with the amount of IPD retrieved.

B. Suggestions For Future Work

While we found moderate success in the acquisition of IPD for a meta-analysis dealing with the effects of exercise training on BMD in adult humans, we cannot generalize as to the success of obtaining IPD from other pharmacologic and nonpharmacologic

interventions. It would appear plausible to suggest that an examination of the ability to retrieve IPD for other interventions is warranted.

C. So What?

Our work to date suggests that while meta-analysis of IPD has the potential for increased statistical power as well as a more thorough examination of potential covariates, this has to be countered with the amount of IPD retrieved.

VI. REFERENCES – Not Applicable

VII. APPENDICES

"Retrieval of Individual Patient Data for an Exercise-Related Meta-Analysis" Article .. **8-23**

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"Progressive Resistance Training and Bone Mineral Density in Women" Article **30-42**

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Retrieval of Individual Patient Data for an Exercise-Related Meta-Analysis

By

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Running Title: Retrieval of Individual Patient Data …

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ABSTRACT

Purpose: To examine the level of success of acquisition of individual patient data (IPD) for a meta-analysis on the effects of exercise on bone mineral density in adults. **Methods:** For the purpose of obtaining IPD, studies were selected from a database that contained 76 studies that met our previously defined meta-analytic inclusion criteria. Initial and follow-up request letters for IPD, separated by approximately five weeks, were sent via postal-mail to the appropriate authors of the 76 studies. All authors who provided IPD were sent $40.00 (US) to help cover expenses. **Results:** Of the 76 eligible studies we were able to obtain data from 29 (38.2%). Binary multiple logistic regression analysis revealed a trend suggesting that authors of studies conducted in the United States were less likely to supply IPD when compared with authors who conducted studies in other countries (adjusted odds ratio = 0.324, 95% confidence interval = 0.104 to 1.004). Only 19.0% of authors from studies conducted in the United States versus 52.9% of authors from other countries provided us with IPD. None of the other variables in this model (gender of author, source of publication, year of publication) were significant predictors for whether IPD were provided. **Conclusions:** The results suggest moderate success in the acquisition of IPD for a meta-analysis dealing with the effects of exercise training on bone mineral density in adults. We were more successful when IPD were requested from studies conducted in countries other than the United States. Given the relatively low response rate, the traditional use of summary data for meta-analysis may be more appropriate for examining the effects of exercise training on bone mineral density in adults.

KEYWORDS: Physical activity, methods, systematic review, epidemiology, bone mineral density

INTRODUCTION

{Paragraph 1}

The use of meta-analysis is becoming increasingly more common in the exercise training and physical activity literature. A recent Medline search by one of the authors (KSK) found that the number of citations listed using the keywords "exercise and meta-analysis" has increased from two between the years 1980-1985 to 121 between the years 1995-2000 (unpublished results). To the best of our knowledge, all meta-analyses on this topic conducted to date have derived their results from the aggregation of summary data provided in the studies. An alternative approach is the retrieval of individual patient data (IPD) from study authors. One of the major advantages of using IPD in a meta-analysis is the potential for increased statistical power as well as a more thorough examination of potential covariates.(2,10,12)The use of IPD may be especially appropriate since many meta-analyses include a small number of studies, thus limiting the interpretation and application of results. However, one of the potential disadvantages with the retrieval of IPD is the inability to obtain IPD from studies that meet one's predefined inclusion criteria. This results in a form of bias known as retrieval bias.(10) Consequently, the use of summary data from individual studies may be preferable.

{Paragraph 2}

We have previously published meta-analytic work from a database consisting of studies dealing with the effects of exercise on bone mineral density in adult humans.(5-9) While our previous work has resulted in some noteworthy findings, these meta-analyses were based on the aggregation of summary data from individual studies. Since the acquisition of IPD could lead to a more accurate determination of the role of exercise on bone mineral density, we sought such

data from study authors. The purpose of this paper is to report on the level of success of acquiring IPD dealing with the effects of exercise on bone mineral density in adult humans.

METHODS

Acquisition of IPD Data

{Paragraph 3}

The acquisition of IPD was conducted according to the general guidelines of Friedenreich.(4) For this study, references for IPD was derived from a database that contained 76 studies that met our previously defined meta-analytic inclusion criteria on the effects of exercise on bone mineral density in adults (references available on request). Prior to sending out our request for IPD, a cover letter and IPD request sheet were developed, reviewed, revised, and approved by the three authors (See Appendix). We then sent, via postal mail, a copy of the cover letter and an IPD data acquisition form to the corresponding authors of the 76 studies. A follow-up request, approximately five weeks later, was sent to all authors who did not respond to our initial request. If the corresponding author referred us to one of the co-authors, contact was made with that author in an attempt to retrieve IPD. The first request contained no deadline date for the receipt of IPD. However, the second request included a deadline date of approximately four weeks from the date of mailing for the receipt of IPD. This deadline was extended for those authors who contacted us to request additional time to provide us with IPD. Some individual patient data were already available from five of the original studies in our database (i.e., from the published tables). However, requests were also sent to the corresponding authors of these studies in the event that additional IPD data might be provided. All authors who supplied IPD were mailed a check for $40.00 (US) to help cover incurred costs. Prior to the start of this study, approval was obtained by the Institutional Review Board at Massachusetts General Hospital.

Statistical Analysis

{Paragraph 4}

Descriptive statistics (frequencies, percentages, ranges, means and standard deviations) were used to report overall results. Binary multiple logistic regression was used to examine potential predictors for whether IPD were finally sent to us or not. Predictors in the model included gender of author contacted, source of publication (journal versus other), country in which the study was conducted (USA versus other), and year of publication. The Likelihood Ratio Statistic and Hosmer and Lemeshow Test were used to identify whether the model adequately fit the data. The Nagelkerke R-squared statistic was used to identify the amount of variance accounted for by the predictor variables. The Nagelkerke R-squared statistic is an adjusted version of the Cox and Snell R-squared. This adjustment was necessary because the Cox and Snell R-squared statistic has a value less than 1 even for a perfect model. Significance of regression coefficients for individual predictor variables was examined using the Wald statistic. In addition, odds ratios and 95% confidence intervals, adjusted for other variables in the model, were used to examine the significance of individual predictor variables. Comparison of models with and without interactions was examined using the G test, which compares the log-likelihoods between two models. The alpha level for a Type I error was set at $P \leq 0.05$. Trends were defined as those values greater than 0.05 but less than or equal to 0.10. (11,13)

Description of Responses

{Paragraph 5}

Of the 76 requests mailed out, 41 (53.9%) authors responded, 33 (43.4%) did not respond at all, and two (2.6%) were returned to us because of undeliverable/invalid addresses. The reasons given by those authors who responded to our request but never supplied IPD data are shown in

Table 1. Of the 41 who did respond, 26 of the 74 total, or 35.1%, provided us with IPD data. Of the 26 authors who provided IPD data, 22 (84.6%) sent their data as an attachment via electronic mail (our suggested preference) while two each sent data via either postal mail (7.7%) or facsimile (7.7%). The average time taken from the date initial letters of request were mailed to the date that data were received ranged from 14 to 89 days ($\bar{x} \pm SD = 50 \pm 23$ days). Of the 22 authors who provided IPD via electronic mail, 15 (68.2%) included their data as a Microsoft Excel® attachment (our suggested preference) while the remaining seven (31.8%) provided data as a SPSS® file. Individual patient data provided from one author (for one study) could not be used because of missing data for bone mineral density and our inability to contact this author at follow-up. Individual patient data from another author (for one study) was also excluded because it was a subset of data from another study already included in our database. Thus, we received usable IPD data for 24 of 76 studies (31.6%) for which data were requested. In addition, we already had in our possession IPD data from a total of five (6.6%) other studies. This left us with 29 studies (38.2%) for future IPD level analysis.

Logistic Regression Analysis

{Paragraph 6}

The results of our binary multiple logistic regression analysis are shown in Table 2. Approximately 21% of the variance was accounted for by the predictor variables ($R^2_{adj} = 0.207$). Both the Likelihood Ratio Statistic ($\chi^2 = 12.046$, $p = 0.017$) and Hosmer and Lemeshow Test ($\chi^2 = 4.660$, $p = 0.793$) demonstrated that the model adequately fit the data. There was a trend for country where the study was conducted (USA versus other) to be a predictor of whether or not IPD were provided, suggesting that authors of studies conducted in the United States were less likely to supply IPD when compared with authors who conducted studies in other countries.

Only 19.0% of authors from the United States versus 52.9% of authors from other countries provided us with IPD. None of the other variables were significant predictors for whether IPD would be provided.

{Paragraph 7}

Since there was a statistically significant association between country and year of publication ($r = 0.330$, $p = 0.004$), we compared our original model with a second model that included the interaction between country and year of publication. No statistically significant difference was found between the two models ($G = 0.464$, $p = 0.496$).

DISCUSSION

{Paragraph 8}

While the acquisition of IPD for meta-analytic purposes can lead to increased statistical power and a more thorough examination of potential covariates, the results of our investigation suggest that obtaining such data from authors of intervention studies dealing with the effects of exercise training on bone mineral density in adults is difficult (31.6% of authors contacted provided IPD). This, coupled with the increased costs associated with the retrieval of IPD (2), suggests that the use of summary data from the actual studies may be more appropriate for examining the effects of exercise training on bone mineral density in adults. More importantly, the inability to acquire IPD results in greater information bias.

{Paragraph 9}

To the best of the authors' knowledge, we are not aware of anyone who has attempted to retrieve IPD for an exercise-related meta-analysis. While the retrieval of IPD for meta-analyses may be problematic across all fields, including exercise, our results suggest that it may be especially problematic for those individuals interested in conducting IPD meta-analyses of exercise and

bone studies. For example, Arnot et al. (1) was able to retrieve IPD from five of seven trials (71.4%) dealing with the effects of preoperative radiotherapy in esophageal carcinoma. Another meta-analysis reported the retrieval of IPD from 39 of 63 studies (61.9%) that met their inclusion criteria on the topic of breast cancer and hormone replacement therapy. (3) This compares to approximately 32% in our study.

{Paragraph 10}

One of the surprising findings of this study was the trend for more authors from studies conducted in countries other than the United States to provide us with IPD. While purely speculative, it may be that authors of studies conducted in the United States were less likely to provide us with IPD because they did not want to take the time to retrieve such information. It may also be that authors in the United States were more concerned about protecting their data because of the potential misuse of such. Since we are not aware of any other work in the meta-analytic field that has focused on predictors for retrieval of IPD, it would seem appropriate to suggest that future research in the meta-analytic field in general, and the exercise and meta-analysis field in particular, focus on this area. This may be especially true since only 21% of the variance was accounted for in our logistic regression model. Thus, it appears that there may be other unknown factors, or combinations of factors, surrounding the retrieval of IPD.

{Paragraph 11}

Since our investigation was limited to studies dealing with the effects of exercise on bone mineral density, it may be inappropriate to generalize our results to other exercise meta-analyses. Therefore, it would appear plausible to recommend that additional studies of this nature be conducted on other topics dealing with such areas as the effects of exercise training on resting blood pressure, self-esteem and anxiety, etc. As a result, this may lead to a better understanding

regarding the use of IPD in selected exercise meta-analyses. In addition, the accumulation of such information may provide information about the feasibility of collecting IPD when conducting an exercise-related meta-analysis.

{Paragraph 12}

In conclusion, the results of our study suggest moderate success in acquiring IPD for a meta-analysis dealing with the effects of exercise training on bone mineral density in adults, and that this success appears to be greater when IPD is requested for studies conducted in countries other than the United States. Given the relatively low response rate, and thus, increased bias, the use of summary data may be more appropriate for examining the effects of exercise training on bone mineral density in adults.

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Conflict of Interest: There are no conflicts of interest for any of the authors with the topic of this study.

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Table 1. Responses of people who responded to our request but never supplied IPD data.

Number of authors	Results/Responses
6	Data no longer available.
2	Data no longer available because of a change in computer systems.
3	Corresponding author did not have data; referred us to another author but never received a response and/or data.
1	Expressed an interest in providing data but never provided such.
1	Did not have time to track down.
1	Not willing to supply data until published in a refereed journal (original source was a dissertation).
1	Not willing to supply data because meta-analysis is inappropriate for exercise and BMD studies.

Table 2. Results for multiple logistic regression analysis (N=74).

Variable	B	SE	df	Significance	Exp(B)	95% CI
Constant	-275.443	190.997	1	0.149	0.000	NA
Country	-1.128	0.577	1	0.051*	0.324	0.104-1.004*
Gender	.246	0.544	1	0.652	1.279	0.440-3.716
Source	.614	1.179	1	0.602	1.848	0.183-18.627
Year	.138	0.096	1	0.146	1.150	0.951-1.385

Notes: B, regression coefficients for the logistic regression; SE, standard error of the regression coefficients; df, degrees of freedom; Exp(B), odds ratio, adjusted for independent variables; 95% CI, 95% confidence interval for the odds ratio; *, trend for statistical significance.

APPENDIX

Date:

Address:

Dear Dr.

Hello! We are currently funded by the United States Army Medical Research and Material Command (USAMRMC-Award #17-98-1-8513) for the purpose of conducting a meta-analysis on the effects of exercise on bone mineral density (BMD) using individual patient data (IPD). Individual patient data meta-analysis differs from the usual meta-analysis in that individual data points are pooled instead of summary statistics (i.e., means, etc.). With this in mind, you have published the following article on exercise and BMD that meets our inclusion criteria:

Reference here:

To include your study in our meta-analysis, we need the information listed on the next page **for each patient.** Would you be willing, at your earliest convenience, via fax, E-mail, or postal mail, to provide us with this patient-level data? Please **DO NOT** send any information (identifiers) that may breech confidentiality agreements that you have with your patients. Any data supplied will be held securely and treated as confidential. **After receiving this data, we will send you a check in the amount of $40.00 to compensate you for your time and effort.** Further, you will be acknowledged as having contributed to the database in any future publications.

If you have any questions, please feel free to contact me personally at any time! Thank you, and we look forward to hearing from you and working with you.

Sincerely yours,

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Thank you ahead of time for your willingness to supply us with the **individual patient data** for our meta-analytic study. We would like to have the following information listed below. While we would prefer to have this information in an Excel Spreadsheet, we will accept the data in any format. Please provide a codebook that defines each of the variables, including the ability to differentiate between exercise and control groups. If no information for some of these variables is available or a variable was not measured, please supply us with whatever information you have for the other variables.

- Bone mineral density (BMD) values for each subject in the study (pre and post). Please tell us the site that was assessed (for example, proximal femur) and the metric used (for example, g/cm^2).
- Age in years for each subject at the beginning of the study (years)
- Ethnicity of each subject in the study (for example, Caucasian, Black, etc.)
- Gender of each subject in the study (male or female)
- Height (centimeters) of each subject in the study (pre and post)
- Body weight (kilograms) of each subject in the study (pre and post)
- Body mass index (kg/m^2) of each subject in the study (pre and post)
- Percent body fat of each subject in the study (pre and post)
- Lean body mass (kilograms) of each subject in the study (pre and post)
- Muscular strength (kilograms) of each subject in the study (pre and post)
- Maximum oxygen consumption (ml/kg/min) of each subject in the study (pre and post)
- Age in years at which each subject experienced menarche
- Number of days that the menstrual cycle lasted for each subject in the study
- Number of years that each subject was postmenopausal prior to taking part in the study
- Calcium intake (milligrams per day) for each subject in the study (pre and post)
- Vitamin D intake (milligrams per day) for each subject in the study (pre and post)
- Phosphorus intake (milligrams per day) for each subject in the study (pre and post)
- Was this subject ingesting any type of estrogen or "estrogen like" containing drugs during the study? (yes or no)
- Did this subject smoke cigarettes? (yes or no)
- Did this subject consume alcohol? (yes or no)
- Did this subject have a previous fracture? (yes or no)
- Compliance of each subject with the exercise protocol (percentage of sessions attended)
- Any other information that you felt was pertinent to the study

You may use any one of the following media to provide us with this data:

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Coding Instructions Sheet for Individual Patient Data

Column #	Code	Description
1	study	Author(s) of study
2	study id	Unique study identification number
3	group	group data is from - coded as exercise or control
4	subject id	Unique subject identification number
5	group_des	Expanded description of group - code as reported
6	site_gen	General site that bone mineral density was assessed - coded as radius, femur spine, wrist, total body other
7	site_spe	Specific site that bone mineral density was assessed - coded as lumbar-1-4, lumbar-2-4, femoral neck, trochanter, intertrochanter, Ward's triangle, distal radius, proximal radius, total body, other
8	other_site	Expanded description of bone mineral density sites assessed - Code as reported
9	I_bmd	Initial bone mineral density (gm/cm/2)
10	f_bmd	Final bone mineral density (gm/cm/2)
11	d_bmd	Difference in bone mineral density (gm/cm/2)
12	pd_bmd	Percent change in bone mineral density
13	use	Rows of data to average? - coded as yes or no
14	age	Age of subjects (years)
15	ht	Height of subjects (cm)
16	I_wt	Initial weight of subjects (kg)
17	f_wt	Final weight of subjects (kg)
18	d_wt	Difference in weight of subjects (kg)
19	I_bm	Initial body mass index (kg/m/2)
20	f_bm	final body mass index (kg/m/2)
21	d_bm	difference in body mass index (kg/m/2)
22	I_fat_c	Initial percent fat (calipers)
23	f_fat_c	Final percent fat (calipers)
24	d_fat_c	Difference in percent fat (calipers)
25	I_fat_d	Initial percent fat (dual energy x-ray absorptiometry or underwater weighing)
26	f_fat_d	Final percent fat (dual energy x-ray absorptiometry or underwater weighing)
27	d_fat_d	Difference in percent fat (dual energy x-ray absorptiometry or underwater weighing)
28	I_lbm	Initial lean body mass (kg)
29	f_lbm	Final lean body mass (kg)
30	d_lbm	Difference in lean body mass (kg)
31	I_vo2	Initial maximum oxygen consumption (ml/kg/min)
32	f_vo2	Final maximum oxygen consumption (ml/kg/min)
33	d_vo2	Difference in maximum oxygen consumption (ml/kg/min)
34	p_vo2	Percent change in maximum oxygen consumption (ml/kg/min)
35	I_hr	Initial resting heart rate (beats/minute)

Coding Instructions Sheet for Individual Patient Data

Column #	Code	Description
36	f_hr	Final resting heart rate (beats/minute)
37	d_hr	Difference in resting heart rate (beats/minute)
38	p_hr	Percent change in resting heart rate
39	men_cyc	Length of menstrual cycle (days)
40	estrogen	Were subjects taking estrogen - coded as yes, no, or nd
41	estrogen2	Number of years subjects were taking estrogen
42	menarche	Age at menarche
43	meno	Menopausal status of subjects - coded as premenopausal, postmenopausal, or nd
44	meno_yrs	Number of years subjects were postmenopausal
45	gender	Gender of subject - coded as female or male
46	race	Race of subject - coded as white, black, hispanic, japanese, chinese, or other
47	smok_1	Did the subjects smoke? Coded as yes, no or nd
48	smok_2	Number of cigarettes smoked by subject each day
49	alcoh_1	Did the subjects consume alcohol? Coded as yes, no, or nd
50	alcoh_2	Number of alcoholic drinks consumed per day by subjects
51	fracture	Did the subjects have previous fractures prior to taking part in the study?
52	str_pc	Percent change in strength of the subjects
53	l_kcal	Initial number of calories consumed per day by subjects
54	f_kcal	Final number of calories consumed per day by subjects
55	d_kcal	Difference in number of calories consumed per day by subjects
56	pd_kcal	Percent difference in the number of calories consumed per day by subjects
57	l_fat	Initial fat intake of subjects (grams)
58	f_fat	Final fat intake of subjects (grams)
59	d_fat	Difference in fat intake of subjects (grams)
60	pd_fat	Percent difference in fat intake of subjects
61	l_cho	Initial cholesterol intake of subjects (milligrams)
62	f_cho	Final cholesterol intake of subjects (milligrams)
63	d_cho	Difference in cholesterol intake of subjects (milligrams)
64	pd_cho	Percent difference in cholesterol intake of subjects
65	l_prot	Initial protein intake of subjects (grams)
66	f_prot	Final protein intake of subjects (grams)
67	d_prot	Difference in protein intake of subjects (grams)
68	pd_prot	Percent difference in protein intake of subjects
69	l_ca	Initial calcium intake of subjects (milligrams)
70	f_ca	Final calcium intake of subjects (milligrams)
71	d_ca	Difference in calcium intake of subjects (milligrams)

Coding Instructions Sheet for Individual Patient Data

Column #	Code	Description
72	pd_ca	Percent difference in calcium intake of subjects
73	I_mg	Initial magnesium intake of subjects (milligrams)
74	f_mg	Final magnesium intake of subjects (milligrams)
75	d_mg	Difference in magnesium intake of subjects (milligrams)
76	pd_mg	Percent difference in magnesium intake of subjects
77	I_phos	Initial phosphorus intake of subjects (milligrams)
78	f_phos	Final phosphorus intake of subjects (milligrams)
79	d_phos	Difference in phosphorus intake of subjects (milligrams)
80	pd_phos	Percent difference in phosphorus intake of subjects (milligrams)
81	I_vitd	Initial vitamin D intake of subjects (I.U.'s)
82	f_vitd	Final vitamin D intake of subjects (I.U.'s)
83	d_vitd	Difference in vitamin D intake of subjects (I.U.'s)
84	pd_vitd	Percent difference in vitamin D intake of subjects
85	I_iron	Initial iron intake of subjects (milligrams)
86	f_iron	Final iron intake of subjects (milligrams)
87	d_iron	Difference in iron intake of subjects (milligrams)
88	pd_iron	Percent difference in iron intake of subjects
89	length	Length of the exercise protocol (weeks)
90	type	Type of training - Coded as weightbearing, non-weightbearing, weight training
91	comply	Percentage of exercise sessions that the subjects attended
92	assess	Type of bone mineral density assessment - Coded as dual energy x-ray absorptiometry (DEXA), dual photon absorptiometry (DPA), singel photon absorptiometry (SPA), quantitative computed tomography (QCT), or other
93	design	Study design coded as randomized controlled trial (RCT) or controlled trial (CT)
94	t_code	Time to code each study (hours and minutes)
95	d_code	Date study was coded

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Research Series Article

Resistance Training and Bone Mineral Density in Women

A Meta-Analysis of Controlled Trials

ABSTRACT

Kelley GA, Kelley KS, Tran ZV: Resistance training and bone mineral density in women: a meta-analysis of controlled trials. *Am J Phys Med Rehabil* 2001;80:65–77.

The purpose of this study was to use meta-analysis to examine the effects of resistance training on bone mineral density at the femur, lumbar spine, and radius in pre- and postmenopausal women. Resistance training had a positive effect on bone mineral density at the lumbar spine of all women and at the femur and radius sites for postmenopausal women. It was concluded that resistance training has a positive effect on bone mineral density in women.

Key Words: Exercise, Bone, Women, Meta-Analysis

Osteopenia and osteoporosis are major public health problems in the United States, affecting primarily lean, white, postmenopausal women.[1] Currently approximately 26.2 million white, postmenopausal women in the United States have either osteopenia or osteoporosis.[1] More specifically, osteopenia, defined as bone density that is 1 to 2.5 SD below the young adult reference range, affects an estimated 16.8 million (54%) of postmenopausal white women in the United States, whereas osteoporosis, defined as bone density >2.5 SD below the young adult reference range, affects another 9.4 million (30%) women.[1, 2] Low-bone density increases the risk for fractures, particularly at the hip, spine, and distal forearm. Currently, the estimated lifetime risk for fracture in 50-yr-old white women in the United States is 17.5% at the hip, 15.6% at the vertebrae, and 16.0% at the distal forearm.[1] In terms of the mortality rate, the survival rate at 5-yr follow-up relative to those of like age and gender is 0.83 for those who have experienced a hip fracture, 0.82 for vertebral fractures, and 1.00 for fractures of the forearm.[3] In the United States,

the estimated cost of fractures can be as high as $20 billion per year, with hip fractures accounting for more than a third of the total cost.[4] Furthermore, because of increased life expectancy, the number of women with low-bone density and subsequent fractures is expected to increase substantially in future years.

Physical activity has been suggested as a nonpharmacologic intervention for maximizing bone density during the younger years and preventing the bone loss during the later years.[5] Recent meta-analyses[6, 7] demonstrated the positive effects of aerobic exercise on both lumbar spine and hip bone mineral density (BMD) in postmenopausal women. Another potentially valuable type of physical activity is resistance training. Resistance training is a low-cost, nonpharmacologic intervention that is available to most of the public. Besides the positive effects on the bone, resistance exercise increases lean-body mass, decreases body fat, and increases muscular strength in both adult men and women.

Unfortunately, traditional narrative reviews on the effects of progressive resistance exercise on BMD have led to conflicting results. For example, seven reviews[8–14] have suggested that progressive resistance exercise *may* have a positive effect on BMD, although nine reviews[15–23] have suggested that progressive resistance exercise *does* have a positive effect. These discrepancies are not surprising given the fact that intervention studies[24–52] examining the effects of resistance exercise on BMD in adults have led to less than overwhelmingly positive results. For example, for the BMD sites assessed in previously mentioned studies, only 20% were reported as statistically significant. One of the possible reasons for the lack of statistically significant findings may be the result of the low statistical power leading to an increased risk of type 2 errors in some studies. Meta-analysis is a quantitative approach in which individual studies addressing a common problem are statistically aggregated.[53, 54] It is especially useful with a small number of subjects in the studies.[54]

As part of a larger study, we[55] previously showed a weight-training-induced improvement of approximately 1% in BMD at all sites combined in postmenopausal women. However, a detailed examination of the effects of progressive resistance exercise on BMD was not conducted. This is also the case with another meta-analysis[56] that combined BMD results from both progressive resistance and aerobic exercise studies. To date, we are unaware of any meta-analysis that has provided a detailed examination of the effects of resistance training on BMD in women. Given the healthcare consequences of low BMD, especially among women, it is important to gain a better understanding of the effects of resistance training on BMD. Thus, the purpose of this study was to use the meta-analytic approach to examine the effects of resistance training on BMD in women.

METHODS

Data Sources

We performed computerized literature searches of articles indexed between January 1966 and December 1998 using MEDLINE, Current Contents, Sport Discus, and Dissertation Abstracts International databases. The following keywords were used either alone or in combinations for computer searches: bone, bone density, bone mineral density, exercise, physical activity, women, females, physical fitness, fitness, weight training, resistance exercise, resistance training, osteoporosis, and osteopenia. The titles and abstracts of studies identified in the computerized searches were examined to exclude irrelevant studies. We retrieved the full text of the remaining articles and we read each paper to determine whether it contained information on the topic of interest. Because computer searches have been shown to yield less than two-thirds of relevant articles,[57] the reference lists from both original and review articles were also reviewed to locate studies that had not been previously identified and which seemed to contain information on the topic of interest. In addition, we also hand searched selected journals. Furthermore, three experts on exercise and BMD (Drs. Charlotte Sanborn, David Nichols, and Christine Snow) reviewed our reference list and coding sheet for thoroughness and completeness.

Study Selection

Inclusion criteria for this study were as follows: (1) randomized or nonrandomized trials that included a comparative nonexercise control group or control period; (2) resistance training, defined as any external resistance added while performing exercises, as the only intervention; (3) adult female humans (mean study age, ≥18 yr) as subjects; (4) journal articles, dissertations, and master's theses published in the English-language literature; (5) studies published and indexed between January 1966 and December 1998; (6) BMD (relative value of bone mineral per measured bone area) assessed at the femur, lumbar spine, or radius; (7) training studies lasting a minimum of 16 wk. Only information that met the above criteria was included in our analysis. Thus, for example, if BMD was also assessed in women performing aerobic exercise, we did not include this information because it did not meet our inclusion criteria. We limited our analysis to the femur, lumbar spine, and radius because they are the most often studied and these areas are the most vulnerable to fracture. Because dissertations may eventually become full-length journal articles, we cross-refer-

enced between the two to avoid duplication. We did not include abstracts and conference papers from national meetings because of the paucity of data provided as well as the inability to obtain complete data from the authors. Studies published in foreign language journals were also not included because of the potential error in the translation and interpretation of findings. Studies that met our inclusion criteria were also examined to ensure that the same subjects were not included in more than one study.[58] For studies that met our inclusion criteria but did not provide appropriate information on changes in BMD,[59, 60] we personally tried to contact the authors to retrieve such information.

Data Extraction

Coding sheets that could hold 242 items were developed and used in this investigation. In addition, coding instructions that described how to code each item on the coding sheet were developed and used. To avoid coding bias, all data were extracted independently by two authors. The authors then met and reviewed every item for accuracy and consistency. Disagreements were resolved by consensus. Blinding of coders to study information in relation to the identity and institutional affiliation of the study authors, as well as study results, were not performed because, according to a recent work,[61] these procedures have neither a clinically nor statistically significant effect on the results. The major categories of variables coded included study characteristics, physical characteristics of subjects, and primary and secondary outcomes.

Statistical Analysis

Primary Outcomes. The primary outcomes in this study were changes in BMD at the femur, lumbar spine, and radius. Because of the various ways in which the authors reported data on changes in BMD and because we also wanted to maximize the number of studies and outcomes that could be included in our analysis, we used the standardized difference approach as our effect size (ES) measure.[62] This was calculated by subtracting the change outcome in the exercise group from the change outcome in the control group, and then dividing this difference by the pooled standard deviation of the exercise and control groups.[62] The ES was then corrected for small-sample bias.[62] For studies that included multiple outcomes because of more than one group (for example, an exercise group that trained at a higher intensity *vs.* one that trained at a lower intensity), net changes in bone mineral density were treated as independent data points.[63] In general, an ES of 0.20 was considered a small effect, 0.50 a moderate effect, and 0.80 a large effect.[64] An ES of 0.20, for example, means that the exercise group differed from the control group by two-tenths of a standard deviation in favor of the exercise group. Because of the small-sample size in this study, especially for subgroup analyses, bootstrap resampling (5,000 iterations) was used to generate 95% BCIs around mean ES changes for BMD.[65] The bootstrap technique is a computer-intensive, nonparametric method of estimating the reliability of the original sample estimate, in this case, ES changes in BMD. By randomly drawing from the available sample, with replacement, samples the same size as the original are generated. Each time an observation is selected for a new sample, each of the elements of the original sample has an equal chance of being selected. This is similar to replicating each member of a sample 5,000 times (iterations). The main advantage of this approach is that the estimate desired is not based on some theoretical distribution, but rather, on the sample itself. This approach frees one from the constraints of the central limit theorem. The number of iterations chosen was based on previous research demonstrating that improvement of estimation accuracy was limited beyond 5,000 iterations.[66] If the 95% confidence interval included zero (0.00), it was concluded that there was no statistically significant effect of exercise on BMD.

Heterogeneity of ES changes in BMD was examined using the Q statistic.[62] A random-effects model was used when changes were significantly heterogeneous ($P < 0.05$), whereas a fixed-effects model was used in the absence of significant heterogeneity.[53] For studies that included multiple outcomes because of more than one group, net changes were treated initially as independent data points. However, to examine the influence (sensitivity) of each study on the overall results, analyses were performed with each study deleted from the model.

Publication bias (the tendency for journals to publish studies that yield statistically significant results and/or authors to only submit studies that yield statistically significant results) was examined using Kendall's tau statistic (τ).[67] A statistically significant result ($P < 0.05$) was considered to be suggestive of publication bias.

Study quality was assessed using a three-item questionnaire designed to assess bias, specifically, randomization, blinding, and withdrawals/dropouts.[68] The number of points possible ranged from a low of 0 to a high of 5. All questions were designed to elicit yes (1 point) or no (0 point) responses. The questionnaire took less than 10 min per study. The questionnaire has been shown to be both valid (face validity) and reliable (researcher interrater agreement, $r = 0.77$, 95% confidence interval = 0.60–0.86).[68]

Subgroup Analyses. For categorical variables, subgroup analyses for primary outcomes were performed using analysis of variance-like procedures for meta-analysis.[62] These procedures provide statistics for both

TABLE 1
Study characteristics

Study	Design/Subjects	Resistance Training Intervention	BMD Assessment
Bouxsein[24]	RCT that included 20 premenopausal women ~20 yr old assigned to either a resistance training (n = 12) or control (n = 8) group	35 wk of training consisting of 14 exercises performed 3 times per week for 3 sets of 8–12 repetitions at 65–85% of 1 RM	DEXA (Hologic) at the lumbar spine (L2-4), femoral neck, trochanter, and Ward's triangle
Chilibeck et al.[25]	CT consisting of 30 premenopausal women assigned to either a resistance training (n = 20; age = 20.3 ± 1.0 yr) or control (n = 10; age = 20.2 ± 0.4 yr) group	20 wk of training consisting of 7 exercises performed 3 times per week for 5 sets of 6–12 repetitions at 70–80% of 1 RM	DEXA (Hologic) at the arms, ribs, thoracic spine, lumbar spine, pelvis, legs, whole body, femoral neck, trochanter, intertrochanter, Ward's triangle, and total hip
Delaney[26]	RCT that included 88 premenopausal women ~28 to 39 yr of age assigned to either a resistance training (n = 46) or control (n = 42) group	20 wk of training consisting of 12 exercises performed 3 times per week for 3 sets of 8–12 repetitions at 70% of 1 RM	DEXA (Lunar) of the lumbar spine (L2-4) and total body; SPA (Lunar) at the radius
Dornemann et al.[27]	RCT consisting of 26 premenopausal women assigned to either a resistance training (n = 12; age = 43 ± 3 yr) or control (n = 14; age = 45 ± 3 yr) group	24 wk of training consisting of 7 exercises performed 3 times per week for 1–5 sets of 4–15 repetitions	DEXA (Hologic) at the lumbar spine, femoral neck, and distal radius
Gleeson et al.[28]	CT that included 72 premenopausal women assigned to either a resistance training (n = 34; age = 33.4 ± 6.3 yr) or control (n = 38; age = 32.7 ± 5.6 yr) group	52 wk of training consisting of 8 exercises performed 3 times per week for 2 sets of 20 repetitions at 60% of 1 RM	DPA (Lunar) at the lumbar spine; SPA (Osteon) at the os calcis
Hartard et al.[29]	CT that included 31 postmenopausal women with osteopenia assigned to either a resistance training (n = 16; age = 63.6 ± 6.2 yr) or control (n = 15; age = 67.4 ± 9.7 yr) group	24 wk of training performed 2 times per week for 1–2 sets of 8–12 repetitions at 70% of 1 RM	DEXA (Norland) at the lumbar spine (L2-4) and femoral neck
Heinonen et al.[30]	CT that included 32 premenopausal women assigned to either a resistance training (n = 13; age = 23.8 ± 5.0 yr) or control (n = 19; age = 25.7 ± 5.2 yr) group	52 wk of training consisting of 2 exercises performed 5 times per week for 5 sets of 10 repetitions at 80% of 1 RM	DEXA (Norland) at the proximal humerus, humeral shaft, radial shaft, ulnar, distal forearm, and calcaneus
Heinonen et al.[31]	RCT that included 53 perimenopausal women 52–53 yrs of age assigned to either a resistance training (n = 26) or control (n = 27) group	78 wk of calisthenics consisting of 8 exercises performed 4 times per week for 3 sets of 16 repetitions with the addition of ankle and wrist bands (1–2 kg)	DEXA (Norland) at the lumbar spine (L2-4), femoral neck, calcaneus, and distal radius
Kerr et al.[32]	RCT that included 42 postmenopausal women 40–70 yr of age assigned to either a muscular strength (n = 23) or muscular endurance (n = 19) group (nonexercising limb served as control)	52 wk of training consisting of 11 exercises performed 3 times per week for 3 sets of 8 repetitions (strength group) or 3 sets of 20 repetitions (endurance group)	DEXA (Hologic) at the femur (trochanter, intertrochanter, femoral neck, Ward's triangle) and radius (ultra distal, mid, and 1/3)
Little[33]	CT that included 10 postmenopausal women assigned to either a resistance training (n = 6; age = 59.5 ± 2.3 yr) or control (n = 4; age = 60.8 ± 1.4 yr) group	32 wk of training consisting of 9 exercises performed 3 times per week for 1 set of 8–12 repetitions at 60–80% of 1 RM	DPA (Lunar) at the lumbar spine (L2-4) and femoral neck; SPA (Lunar) at the distal radius
Lohman et al.[34]	RCT that included 56 premenopausal women assigned to either a resistance training (n = 22; age = 34.2 ± 2.6 yr) or control (n = 34; age = 34.4 ± 3.8 yr) group	78 wk of training consisting of 12 exercises 3 times per week for 3 sets of 8–12 repetitions at 70–80% of 1 RM	DEXA (Lunar) at the lumbar spine (L2-4), femoral neck, trochanter, Ward's triangle, and radius
Mayoux-Benhamou et al.[35]	RCT that included 33 postmenopausal women assigned to either a psoas training (n = 21; age = 58.2 ± 3.4 yr) or control (n = 12; age = 58.9 ± 1.3 yr) group	156 wk of daily psoas training consisting of 2–3 sets of 60 daily hip flexions with 5 kg on the knee	QCT (Elscint) at the lumbar spine (L1-4)

TABLE 1
Continued

Study	Design/Subjects	Resistance Training Intervention	BMD Assessment
Nelson et al.[36]	RCT that included 39 postmenopausal women assigned to either a resistance training (n = 20; age = 61.1 ± 3.7 yr) or control (n = 19; age = 57.3 ± 6.3 yr) group	52 wk of training consisting of 5 exercises performed 2 times per week for 3 sets of 8 repetitions at 80% of 1 RM	DEXA (Lunar) at the lumbar spine (L2-4) and femoral neck
Nichols et al.[37]	RCT that included 17 postmenopausal women at least 60 yr of age assigned to either an exercise (n = 9) or control (n = 7) group	52 wk of training consisting of 8 exercises performed 3 times per week for 3 sets of 10–12 repetitions at 80% of 1 RM	DEXA (Lunar) at the lumbar spine (L2-4), femoral neck, and trochanter
Notelovitz et al.[38]	RCT that included 20 surgically menopausal women assigned to either an estrogen + resistance training (n = 9; age = 43.3 ± 9.6 exercise yr) or estrogen + no exercise (n = 11; age = 46.2 ± 6.8 yr) group	52 wk of training consisting of up to 11 exercises performed 3 times per week for 8 repetitions per exercise	DPA (Lunar) at the spine as well as total body; SPA (Lunar) at the radius
Payne[39]	CT that included 48 premenopausal women assigned to either a resistance training (n = 28; age = 24.6 ± 9.2 yr) or control (n = 20; age = 22.8 ± 6.1 yr) group	18 wk of training consisting of 9 exercises performed 3 times per week for 1–6 sets of 6–10 repetitions per exercise	DEXA (Lunar) at the lumbar spine (L2-4), femoral neck, Ward's triangle, trochanter, and total body
Preisinger et al.[40]	RCT that included 58 postmenopausal women assigned to either an exercise (n = 27; age = 62.6 ± 5.9 yr) or control (n = 31; age = 59 ± 8 yr) group	208 wk of training consisting of 3 exercises performed 3 times per week for 3 repetitions	SPA (Osteodensitometer) at the mid and distal forearm
Protiva[41]	CT that included postmenopausal women 74–94 yr of age observed during a 6-mo control period (n = 13) and then assigned to 9 mo of resistance training (10 of the 13 completed the training along with an additional five subjects)	36 wk of training that included 8 exercises performed 3 times per week for 1–2 sets of 6–12 repetitions while wearing a weighted vest	DEXA (Hologic) at the femoral neck, trochanter, hip, and whole body
Pruitt et al.[42]	CT that included 26 postmenopausal women assigned to either a resistance exercise (n = 17; age = 53.6 ± 4.1 yr) or control (n = 9; age = 55.6 ± 2.9 yr) group	36 wk of training that included 11 exercises performed 3 times per week for one set of 10–15 repetitions at 50–60% of 1 RM	DPA (Lunar) at the lumbar spine (L2-4) and femoral neck
Pruitt et al.[43]	RCT that included 26 postmenopausal women assigned to either high-intensity resistance training (n = 8; age = 67 ± 0.5 yr), low-intensity resistance training (n = 7; age = 67.6 ± 1.4 yr) or control (n = 11; age = 69.6 ± 4.2 yr) group	52 wk of training that included 10 exercises performed 3 times per week for either 2 sets of 7 repetitions at 80% of 1 RM (high-intensity) or 3 sets of 14 repetitions at 40% of 1 RM (low-intensity)	DEXA (Hologic) at the lumbar spine (L2-4) and total hip (femoral neck, trochanter, and Ward's triangle)
Rockwell et al.[44]	CT that included 17 premenopausal women assigned to either a resistance training (n = 10; age = 36.2 ± 3.9 yr) or control (n = 7; age = 40.4 ± 11.5 yr) group	36 wk of training that included 8 exercises performed 2 times per week for 2 sets of 12 repetitions at 70% of 1 RM	DEXA (Lunar) at the lumbar spine and femoral neck
Shaw and Snow[45]	CT that included 40 postmenopausal women assigned to either a resistance training (n = 18; age = 64.2 ± 5.8 yr) or control (n = 22; age = 62.5 ± 6.6 yr) group	36 wk of training that included 6 exercises performed 3 times per week for 3–5 sets of 10–15 repetitions while wearing a weighted vest. Subjects also performed jumping exercises with a weighted vest.	DEXA (Hologic) at the lumbar spine (L2-4) and femoral neck
Sinaki et al.[46]	RCT that included 67 premenopausal women 30–40 yr of age assigned to either a resistance training (n = 32) or control (n = 35) group	156 wk of training that included exercises performed 3 times per week for 3 sets of 10 repetitions	DEXA (Hologic) at the lumbar spine (L2-4), trochanter, femoral neck, and Ward's triangle

TABLE 1
Continued

Study	Design/Subjects	Resistance Training Intervention	BMD Assessment
Sinaki et al.[47]	RCT that included 65 postmenopausal women assigned to either a resistance training (n = 34; age = 55.6 ± 4.5 yr) or control (n = 31; age = 56.5 ± 4.5 yr) group	104 wk of back extension exercise performed 5 times per week for 1 set of 10 repetitions at 30% of maximal isometric back muscle strength	DPA at the lumbar spine (L2-4)
Smidt et al.[48]	RCT that included 49 postmenopausal women assigned to either a resistance training (n = 22; age = 56.6 ± 6.6 yr) or control (n = 27; age = 55.4 ± 8.0 yr) group	52 wk of training that included 3 exercises performed 3–4 times per week for 3 sets of 10 repetitions at 70% of 1 RM	DPA at the lumbar spine (L2-4), femoral neck, Ward's triangle, and trochanter
Snow-Harter et al.[49]	RCT that included 20 premenopausal women approximately 20 yr old assigned to either a resistance training (n = 12) or control (n = 8) group	32 wk of training that included 14 exercises performed 3 days per week for 3 sets of 8–12 repetitions at 65–85% of 1 RM	DEXA (Hologic) at the lumbar spine (L2-4), femoral neck, trochanter, and Ward's triangle
Taafe et al.[50]	RCT that included 25 postmenopausal women assigned to either a high-intensity resistance training (n = 7; age = 67.0 ± 0.5 yr), low-intensity resistance training (n = 7; age = 67.6 ± 1.3 yr), or control (n = 11; age = 69.6 ± 4.3 yr) group	52 wk of training that included 3 exercises performed 3 days per week for either 3 sets of 14 repetitions at 40% of 1 RM (low-intensity) or 2 sets of 7 repetitions at 80% of 1 RM (high-intensity)	DEXA (Hologic) at the femur and middle third of the femur
Thorvaldson[51]	RCT that included 50 postmenopausal women assigned to either a resistance training (n = 12; age = 54.6 ± 2.1 yr) or control (n = 21; age = 54.6 ± 2.1 yr) group	24 wk of training that included 6 exercises performed 3–5 days per week for 3 sets of 10 repetitions	DEXA (Hologic) at the lumbar spine (L1-4) and femoral neck; QCT at the distal radius
Vuori et al.[52]	CT that included 24 premenopausal women assigned to either a resistance exercise (n = 12; age = 21.0 ± 2.5 yr) or control (n = 12; age = 22.0 ± 3.0 yr) group	52 wk of training that included leg press exercise performed 5 times per week for 5 sets of 10 repetitions at 80% of 1 RM	DEXA (Norland) at the lumbar spine, femoral neck, distal femur, patella, proximal tibia, and calcaneus

RCT, randomized controlled trial; CT, controlled trial; subjects; ages reported as mean ± SD; number of subjects listed includes only those who completed the study; BMD, bone mineral density; 1 RM, one repetition maximum; DEXA, dual-energy x-ray absorptiometry; DPA, dual photon absorptiometry; SPA, single photon absorptiometry; QCT, quantitative computed tomography.

within (Q_w) and between (Q_b) group differences. If statistically significant within-group (Q_w) heterogeneity existed ($P < 0.05$), a random-effects model was used. If no statistically significant within-group (Q_w) heterogeneity existed, a fixed-effects model was used. ES changes in BMD were examined initially when the data were partitioned according to study design (randomized vs. nonrandomized), country in which the study was conducted (United States vs. other), study quality (0–2 vs. 3–5), menopausal status (pre vs. post), calcium supplementation, changes in dietary intake during the study, drugs that could affect BMD, and physical activity habits of subjects. For the femur site, we also examined changes in BMD with data partitioned according to the femoral neck, trochanter, intertrochanter, and Ward's triangle. We were unable to examine specific sites at the lumbar spine and radius because of insufficient data. Bootstrap resampling (5,000 iterations) was used to generate 95% confidence intervals around ES changes for all subgroups. Randomization tests (5,000 iterations) were used to generate probability values for between-group differences.[69] Randomization tests using 5,000 iterations can detect a probability as low as 0.002.[69]

Regression Analysis. For continuous variables, potential associations with ES changes in BMD were conducted using meta-regression procedures, calculated with each ES weighted by the reciprocal of its variance, according to procedures described by Hedges and Olkin.[62] This model yields a test of the significance of each predictor (Q_R) as well as a test of model specification (Q_E) which assesses whether systematic variation remains unexplained in the regression model. Thus, a statistically significant Q_R value means that the variables included in the regression are significantly related to the variable of interest, whereas a nonsignificant Q_E value means that the model is well specified. Continuous variables that were examined included percentage

of dropout (number of subjects who did not complete the study), age, height, initial as well as changes in body weight, body mass index, percentage of body fat and lean-body mass, changes in muscular strength, initial BMD, calcium intake, years postmenopausal, length and intensity of training, number of exercises performed, and compliance, defined as the percentage of exercise sessions attended by the subjects.

Secondary Outcomes. Secondary outcomes (changes in body weight, body mass index, percentage of body fat, and lean-body mass) were calculated as the difference (exercise minus control) of the changes (initial minus final) in these mean values. The original metric was used for all secondary outcomes. For those studies in which variance estimation was necessary, these were accomplished using the same procedures as those for estimating variances for BMD.[63] Fixed and random effects models were used following the same procedures as those previously described for BMD. Percentage of changes in muscular strength (one repetition maximum) were reported separately for exercise and control groups.

Unless otherwise noted, all results are reported as mean ± SD. The α level for statistical significance was set at $P < 0.05$. Values between 0.05 and 0.10 were considered as a trend toward statistical significance. Bonferroni adjustments were not made because of the increased risk of a type 2 error.

RESULTS

Study Characteristics

Thirty-one studies met the criteria for inclusion.[24–52, 59, 60] However, we were unable to include two studies[59, 60] because of the inability to obtain data necessary for the calculation of an ES. Thus, we had a 6% loss that met our inclusion criteria. One study[70] was excluded because it included some of the same subjects from another study that we included.[40] A general description of the 29 included studies is shown in Table 1 and the physical characteristics of the exercise and control group subjects are described in Table 2. The per person time to code each study once ranged from 0.58 to 4.67 hr (1.26 ± 0.79 hr). Study quality ranged from 1 to 4 (2 ± 1). The 29 included studies represented 94 ES (femur = 53, lumbar spine = 24, radius = 17) from 61 groups (32 exercise, 29 control). Twenty-three studies were published in journals,[25, 27–32, 34–38, 40, 42–50, 52] five were dissertations,[24, 26, 33, 39, 41] and one was a master's thesis.[51] Twenty studies were conducted in the United States,[24, 26–28, 33, 34, 36–39, 41–50] three in Finland,[30, 31, 52] two each in Austria[29, 40] and Canada,[25, 51] and one each in Australia[32] and France.[35] Percentage of dropout, defined as the number of subjects who did not complete the study, ranged from 0 to 63% in the exercise groups (28 ± 17%) and 0 to 69% in the control groups (17 ± 18%). Thus, pre and post measures of BMD were available for 572 subjects who served as exercisers and 551 subjects who served as controls. The minimum and maximum number of subjects in the exercise groups was 6 and 46 (18 ± 10), respectively, whereas the minimum and maximum number of subjects in the control groups was 7 and 42 (19 ± 10), respectively. For the 14 studies that reported information on race, 12 reported that all of the subjects were white,[26, 28, 33–36, 40, 43, 45–48] one study reported that the subjects were white and black,[42] and another reported that the subjects were white and Asian.[51] For the 18 studies that reported information on calcium supplementation during the study, eight studies reported that some subjects were taking supplements,[33, 36–38, 43, 46, 48, 51] seven reported that all of the subjects were taking supple ments,[24, 26–28, 34, 44, 49] and three reported that none of the subjects were taking supplements.[35, 39, 47] For the 23 studies that reported on whether subjects were taking any type of pharmacologic interventions that could affect BMD, 14 reported that none were taking any pharmacologic interventions,[26, 27, 32–37, 40, 42, 44, 46, 47, 51] eight reported that some were,[25, 28, 30, 31, 39, 43, 45, 48] and one study reported that all were.[38] Ten studies reported that none of the subjects smoked cigarettes,[25, 31, 33, 36, 39, 40, 44–47] whereas four reported that some subjects smoked.[28, 35, 48, 51] Two studies reported that some of the subjects consumed alcohol.[25, 48] Ten studies reported that none of the subjects had been previously active,[25, 26, 29, 31, 33, 34, 36, 39, 40, 43] eight reported that some were,[24, 28, 32, 35, 44, 48–50] and five reported that all were.[30, 37, 46, 51, 52] Five studies reported that none of the subjects had suffered previous fractures,[29, 39, 43, 46, 47] whereas three reported that some had.[33, 36, 40] Compliance, defined as the percentage of resistance training sessions that the exercise groups attended, ranged from 44% to 96% (79 ± 13%). Reliability for BMD assessment (coefficient of variation) ranged from approximately 0.6% to 4% at the femur, 0.6% to 5.0% at the lumbar spine, and 0.5% to 5% at the radius.

Primary Outomes

Initial BMD values for exercise and controls are shown in Table 3, whereas ES changes in BMD are shown in Table 4. BMD values were available for a total of 743 subjects at the femur (392 exercise, 351 control), 870 at the lumbar spine (450 exercise, 420 control), and 441 at the radius (219 exercise, 222 control). Because there was no statistically significant heterogeneity at any of the sites observed, a fixed-effects model was used for overall results at all three sites.

TABLE 2
Initial physical characteristics of subjects

Variable	Exercise n	Exercise (Mean ± SD)	Control n	Control (Mean ± SD)
Age (yr)	32	49.0 ± 17.9	29	47.7 ± 17.8
Height (cm)	27	163.2 ± 2.3	24	163.3 ± 2.8
Weight (kg)	30	63.5 ± 3.7	27	64.4 ± 3.3
BMI (kg/m^2)	28	23.9 ± 1.6	25	24.3 ± 1.5
Fat (%)	13	31.6 ± 5.8	12	31.7 ± 5.8
Lean mass (kg)	12	42.4 ± 3.3	11	42.4 ± 3.7
Postmenopausal (yr)	13	8.6 ± 4.7	12	8.5 ± 4.0
Calcium (mg)	16	926 ± 227	14	825 ± 114

n, number of groups reporting data; BMI, body mass index.

Proximal Femur. Small and statistically insignificant changes in BMD were observed at the femur site. These changes were equivalent to a 0.33% increase in the exercise groups and a 0.05% decrease in the control groups. No evidence of publication bias was observed (r = 0.12, P = 0.26). With each study deleted from the model once, ES changes in BMD at the femur ranged from a low of 0.02 ± 0.37 (95% Bootstrap Confidence Interval [BCI], −0.07–0.11) to a high of 0.09 ± 0.36 (95% BCI, 0.03–0.17). Approximately 90% of the 53 ESs were reported by the authors of the original studies as not being statistically significant.

Lumbar Spine. Small but statistically significant ES changes in BMD were found at the lumbar spine. These changes were equivalent to a 0.19% decrease in the exercise groups and a 1.45% decrease in the control groups. No evidence of publication bias was observed (r = −0.08, P = 0.62). With each study deleted from the model once, ES changes in BMD ranged from a low of 0.19 ± 0.37 (95% BCI, 0.09–0.33) to a high of 0.27 ± 0.36 (95% BCI, 0.14–0.41). Approximately 67% of the 24 ESs were reported by the authors of the original studies as not being statistically significant.

Radius. Small and statistically significant ES changes in BMD were observed at the radius. ES changes were equivalent to a 1.22% increase in BMD for the exercise groups and a 0.95% decrease in the control groups. No evidence of publication bias was observed (r = 0.17, P = 0.38). With each study deleted from the model once, ES changes in BMD at the radius ranged from a low of 0.19 ± 0.36 (95% BCI, 0.03–0.45) to a high of 0.33 ± 0.34 (95% BCI, 0.16–0.52). Approximately 65% of the 17 ESs were reported by the authors of the original studies as not being statistically significant.

Subgroup Analysis

Subgroup analyses for those variables in which there were statistically significant differences or trends for statistically significant differences between groups are shown in Table 5.

Femur. There was a trend for greater ES changes in BMD at the femur when studies were of higher vs. lower quality. Higher-quality studies yielded ES changes that were equivalent to a 1.03% increase in BMD in the exercise groups and a 0.16% increase in the control groups. Lower-quality studies yielded ES changes that were equivalent to a 0.21% increase in the exercise groups and a 0.09% decrease in the control groups. There was also a trend for greater ES changes in BMD at the femur when subjects were postmenopausal vs. premenopausal. For postmenopausal women,

TABLE 3
Initial BMD values

Variable	Studies (n)	Exercise Subjects (Mean ± SD)	Exercise Values (n)	Exercise (g/cm^2) (Mean ± SD)	Control Subjects (Mean ± SD)	Control Values (n)	Control (g/cm^2) (Mean ± SD)
Femur	22	18 ± 8	53	0.852 ± 0.197	16 ± 9	46	0.832 ± 0.178
Lumbar spine	23	20 ± 10	24	1.075 ± 0.115	18 ± 11	23	1.071 ± 0.121
Radius	10	22 ± 14	17	0.497 ± 0.153	22 ± 11	14	0.513 ± 0.160

BMD, bone mineral density; BMD data based on number of exercise and control values.

TABLE 4
BMD results

Variable	Studies (*n*)	Subjects (Mean ± SD)	ES (*n*)	ES (Mean ± SD)	BCI (95%)	Q (*P*)
Femur	22	34 ± 16	53	0.07 ± 0.36	−0.02to0.15	43.81 (0.78)
Lumbar spine	23	38 ± 20	24	0.24 ± 0.36	0.11to0.38[a]	20.68 (0.60)
Radius	10	44 ± 24	17	0.30 ± 0.33	0.13to0.48[a]	23.69 (0.10)

[a] Statistically significant.
BMD, bone mineral density; ES, effect size; BCI, Bootstrap Confidence Interval, Q (*P*), heterogeneity (probability for alpha).

ES changes in BMD were equivalent to a 0.40% increase in the exercise groups and a 0.21% decrease in the controls. For premenopausal women, ES changes were equivalent to a 0.26% increase in the exercise groups and a 0.13% increase in the control groups. No statistically significant between-group differences were found when data were partitioned according to study design, country in which the study was conducted, calcium supplementation, previous physical activity habits, type of BMD assessment, and different sites at which BMD was assessed. Insufficient data were available to examine differences in BMD at the femur when data were partitioned according to diet as well as drugs that could affect BMD.

Lumbar Spine. No statistically significant between-group differences were observed for ES changes at the lumbar spine when data were partitioned according to source of study, country in which the study was conducted, study design, menopausal status of subjects, calcium supplementation, previous physical activity, and type of BMD assessment. Insufficient data were available to examine between-group differences in BMD when data were partitioned according to study quality, drugs that could affect BMD, diet, and sites at which the lumbar spine BMD was assessed.

Radius. There was a trend for greater ES changes in BMD at the radius when studies were of higher vs. lower quality. Higher-quality studies yielded ES changes that were equivalent to a 0.82% increase in BMD in the exercise groups and a 1.87% decrease in the control groups. Lower-quality studies yielded ES changes that were equivalent to a 1.75% increase in BMD in the exercise groups and a 0.23% increase in the control groups. ES changes at the radius were also greater in postmenopausal vs. premenopausal women. For postmenopausal women, ES changes were equivalent to a 1.71% increase in BMD in the exercise groups and a 1.39% decrease in the control groups. For premenopausal women, ES changes were equivalent to a 0.17% increase in the exercisers and a 0.01% increase in the controls. No statistically significant differences

TABLE 5
Subgroup analyses

Variable	Studies (*n*)	Subjects (*n*)	ES (*n*)	ES (Mean ± SD)	BCI (95%)	Q_b (*P*)
Femur						
Study quality						
0–2	21	682	45	0.03 ± 0.37	−0.07–0.10	3.05 (0.08)[a]
3–5	1	61	8	0.24 ± 0.37	0.03–0.44	
Menopausal status						
Premenopausal	9	309	28	−0.01 ± 0.36	−0.16–0.09	2.34 (0.09)[a]
Postmenopausal	12	381	24	0.15 ± 0.38	0.03–0.28	
Radius						
Study quality						
0–2	7	296	8	−0.01 ± 0.38	−0.09–0.05	14.11 (0.001)[b]
3–5	3	145	9	0.56 ± 0.36	0.38–0.75	
Menopausal status						
Premenopausal	4	202	5	−0.02 ± 0.42	−0.13–0.05	9.99 (0.004)[b]
Postmenopausal	5	186	11	0.52 ± 0.36	0.33–0.71	

ES, effect size; BCI, Bootstrap Confidence Interval; Q_b, difference between groups.
[a] Trend for statistical significance when P ranges from ≥0.05 to ≤0.10; [b] Statistically significant when $P < 0.05$.
ES outcomes based on number of ESs.

were observed when data were partitioned according to source of study, country in which the study was conducted, study design, previous physical activity habits, and type of BMD assessment. Insufficient data were available to examine between-group differences in BMD when data were partitioned according to calcium supplementation, drugs that could affect BMD, diet, and different sites at which BMD of the radius was assessed.

Regression Analyses

Femur. The only significant predictor for ES changes in BMD at the femur was changes in the percentage of fat ($Q_R = 6.67$, $P = 0.03$; $Q_E = 14.32$, $P = 0.35$). Larger ES changes in BMD at the femur were observed among subjects with smaller changes in the percentage of fat. No other statistically significant associations were observed.

Lumbar Spine

No significant predictors were observed for ES changes in BMD at the lumbar spine.

Radius. The only significant predictor for ES changes in BMD at the radius was initial lean-body mass ($Q_R = 6.76$, $P = 0.009$; $Q_E = 9.26$, $P = 0.41$). Smaller ES changes in BMD at the radius were observed among subjects with higher initial levels of lean-body mass. Insufficient data were available to examine the relationship between ES changes in BMD and changes in the percentage of body fat and lean-body mass.

Secondary Outcomes

Statistically significant decreases were observed for the percentage of body fat ($-2 \pm 2\%$; 95% BCI, -3 to -1%), whereas there was a statistically significant increase in lean-body mass (2 ± 1 kg; 95% BCI, 1–2 kg). No statistically significant changes were observed for body weight or body mass index. There was a 40% increase in muscular strength in the exercise groups and a 6% increase in the control groups.

DISCUSSION

Implications for Practice

The overall results of this study suggest that across all groups of women included in this analysis, resistance training helps to preserve lumbar spine BMD. Resistance training also seems to increase and preserve BMD at the femur and radius sites in postmenopausal women. Furthermore, with the exception of changes in BMD at the proximal femur, these results were consistent after deletion of each study once from our models.

An interesting finding of this study is the fact that the largest effect on BMD occurred at the radius site in postmenopausal women. One possible reason for this may be the fact that most subjects included in these studies were able to ambulate. Consequently, they may have had greater daily loading placed on the lumbar spine and femur vs. the radius before participation in the studies. Therefore, there may have been an opportunity for resistance training to have a greater effect on BMD at the radius vs. the lumbar spine and femur. However, it may also be that the resistance training programs placed greater relative loads on the radius vs. the lumbar spine and femur sites. The larger changes observed in BMD at the femur when changes in the percentage of fat were smaller as well as the smaller changes at the radius when initial lean-body mass was higher are supportive of the fact that in general, women who weigh more place greater stress on their bones. Thus, heavier women may not experience the same improvements in BMD as leaner women.

Although it seems that postmenopausal women may have the most to gain from a program of resistance training, this form of intervention should almost always be encouraged across all age groups, especially because of other benefits that can be derived from participation in such activities. For example, in this investigation, we saw statistically significant improvements in body composition (decreases in the percentage of body fat and increases in lean-body mass). However, we believe that it is unrealistic to think that any optimal training program (resistance, exercises, sets, repetitions, length of rest intervals, total workload) will ever be developed for maximizing BMD. The best that can occur is some minimal levels to achieve the desired changes. However, even these recommendations are imprecise. For example, despite the various training protocols used in the studies included in this meta-analysis, the deletion of each study once from the analysis had little effect on the overall results. Thus, the best recommendation we can make at this time is to adhere to the general principles of specificity and overload when prescribing resistance training programs aimed at maintaining and/or improving BMD.[5]

Although it is encouraging that resistance training seems to have positive effects on BMD at the lumbar spine, femur, and radius, the clinical importance of such small effects is not known, especially as it relates to fracture risk. We are not aware of any randomized trial(s) that have proven that resistance training reduces the risk of fracture. However, it may be that other factors contribute to increases in bone strength and subsequent reductions in fracture risk. For example, a recent animal study[71] found that mechanical loading improves bone strength by reshaping the bone structure with no apparent increase in BMD. Thus, resistance training may have a similar effect in humans.

Because most of the studies included in this meta-analysis examined the efficacy (does the treatment

work?) of resistance training for enhancing BMD in women, the effectiveness (does the treatment work in the real world?) of such an intervention could be questioned. This may be especially important given the fact that in the United States only 16% of people between the ages of 18 and 64 yr report regular participation in progressive resistance exercise.[72] It may be that other forms of therapy (calcium and/or vitamin D supplementation, hormone replacement therapy, selective estrogen receptor modulators, bisphosphonates) not only have a greater impact on BMD, but they also reduce the risk of fracture. For example, a recent meta-analysis[73] examined over a 3-yr period the effects of 10 mg of alendronate on BMD in osteoporotic women between the ages of 42 and 85 yr. The authors reported increases in BMD of 8.8% at the spine, 7.8% at the trochanter, and 5.9% at the femoral neck. The estimated cumulative incidence of nonvertebral fractures after 3 yr was 12.6% in the placebo group and 9.0% in the alendronate-treated group. It was concluded that administration of alendronate reduces the risk of nonvertebral fractures in osteoporotic postmenopausal women. Given the former, resistance training in conjunction with other types of nonpharmacologic and/or pharmacologic therapy may be most appropriate, especially for those women with osteoporosis.

Implications for Research

One of the surprising findings of this study was the fact that changes in BMD were greater in studies of higher quality. It is generally believed that studies of higher quality yield less positive results than studies of lower quality. For example, a recent study,[74] using the same quality rating scale as ours, examined the impact of study quality on outcomes in placebo-controlled trials of homeopathy. These authors[74] concluded that studies of higher methodologic quality produced less positive results. However, it may be possible that trials with good designs reduce random variability and allow the intervention to produce a larger ES. This may have been the case with our investigation.

The fact that we included both randomized and nonrandomized controlled trials in our study could be questioned. It is generally felt that randomized trials yield results that are more conservative when compared with nonrandomized trials. However, because we did not find a statistically significant difference between any of our outcomes when the data were partitioned by study design, we felt it was appropriate to include both in our analysis.

Although it is important to conduct many statistical tests when performing a meta-analysis, some of our statistically significant results may have been the result of chance vs. any real effect. However, we believe that a greater risk existed of committing a type 2 error if Bonferroni adjustments were made to our data. Thus, our data were analyzed without any type of Bonferroni adjustments.

Although some may feel that the inclusion of dissertations and master's theses which have not been published as journal articles is inappropriate because they lack the same "rigor," we believe that it is critical, given appropriate resources, to include such because of the reported publication bias that has been shown to exist in the literature.[75, 76] For example, Stern and Simes[76] found that approximately 96% of selected psychology journals and 85% of selected medical journals published studies that yielded a statistically significant result. The inclusion of unpublished data represents a feeling that is shared by the majority of meta-analysts and methodologists, as a study by Cook and colleagues[77] has shown that approximately 80% feel that unpublished material such as dissertations and master's theses should definitely or probably be included in scientific overviews.

Despite the knowledge that studies can be more objectively evaluated using the meta-analytic vs. traditional, narrative approach, potential problems still exist. In general, the very nature of meta-analysis dictates that the meta-analysis itself inherits those limitations that exist in the literature. Therefore, the meta-analyst must point out these limitations and provide directions for future research. One of the common problems in meta-analysis is the issue of missing data for outcomes other than the primary ones of interest. For example, the fact that insufficient data were available to perform subgroup analysis on BMD at different lumbar and radius sites could have impacted our results. Although the inability to compare BMD at different lumbar and radius sites was more a function of a lack of sample size vs. the absence of reporting such information, additional studies directed at these sites would seem appropriate. In addition, we would suggest that future studies dealing with the effects of resistance training on BMD in women do a better job of assessing and reporting on the dietary habits of their subjects as well as the types of pharmacologic interventions that these subjects may be taking. Furthermore, because few studies included an assessment of the alcohol and calcium intake of the subjects, greater attention to these in the future seem warranted. It is also recommended that future studies include an evaluation of their data using both an analysis-by-protocol as well as an intention-to-treat approach. As a result, one may examine both the efficacy and effectiveness of resistance training for enhancing BMD in women. This will help provide clinicians with more meaningful information regarding the use of resistance training for enhancing BMD in women. Additional information regarding appropriate study design when examining the effects of exercise on BMD may be found in the excellent review of Snow

et al.[78] Finally, it would seem plausible to suggest that a need exists for a large randomized trial that examines the effect of resistance training on both BMD and fracture risk. However, a trial of this nature may never be successfully conducted.

In conclusion, the results of this meta-analysis suggest that resistance training has a positive effect on the BMD of all women at the lumbar spine, and in postmenopausal women at the femur and radius.

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George Kelley, MD
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Dear Dr. Kelley:

Your manuscript entitled "Aerobic Exercise and Regional Bone Density in Women: A Meta-analysis of Controlled Trials" has been accepted for publication in the *American Journal of Medicine & Sports.*

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Aerobic Exercise and Regional Bone Density in Women: A Meta-Analysis of Controlled Trials

By

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ABSTRACT

The purpose of this study was to use the meta-analytic approach to examine the effects of aerobic exercise on regional bone mineral density (BMD) at the lumbar spine, femur, and radius in women. Twenty-four studies representing 58 groups (31 exercise, 27 control) and 1,029 subjects (517 exercise, 512 control) met the criteria for inclusion. Using a random-effects model, small but statistically significant effect size (ES) changes in BMD were observed at the lumbar spine ($\bar{x} \pm SD = 0.33 \pm 0.49$, 95% confidence interval = 0.16 to 0.50) and femur ($\bar{x} \pm SD = 0.25 \pm 0.35$, 95% confidence interval = 0.14 to 0.35). Changes in lumbar spine BMD were equivalent to a 0.37% increase in the exercise groups and a 1.87% decrease in the control groups. For the femur, changes were equivalent to 1.37% increase in the exercise groups and a 0.58% decrease in the control groups. No statistically significant changes were observed at the radius ($\bar{x} \pm SD = 0.10 \pm 0.45$, 95% confidence interval = -0.20 to 0.41). The overall results of this study suggest that aerobic exercise has a small but positive effect on BMD at the lumbar spine and femur in women.

Medical Subject Headings (MeSH): exercise, physical fitness, bone, bone density, bone mineral density, meta-analysis, systematic review

BACKGROUND

Osteoporosis, defined as abnormally low bone mass, is a major public health problem in the United States as well as other countries. In 1996, it was estimated that approximately 23 million women in the United States had osteoporosis or were at risk for developing the disease. [1] By the year 2015 this figure is expected to increase to approximately 35 million. [2] It is well established that low bone mineral density (BMD) is associated with increased fracture risk. The health-care costs associated with osteoporotic fractures has been reported to exceed 13.8 billion dollars annually.[3] Given the health and economic costs associated with osteoporosis, a need exists for appropriate nonpharmacologic and pharmacologic interventions for dealing with this disease. One such nonpharmacologic intervention may be aerobic exercise,[4] a cheap, low-cost intervention that is available to most of the general public.

We have previously reported that aerobic exercise might help to maintain and/or increase BMD in postmenopausal women but that additional studies were needed before any firm conclusions could be reached.[5-7] Since the time of these published meta-analyses, a number of additional studies have been conducted and/or located. It is critical that up-to-date meta-analyses be performed in order to provide the most recent information possible on the state of knowledge regarding the topic of interest. Given the health-care consequences of low BMD, it is important to understand the role that aerobic exercise may play as a nonpharmacologic intervention for enhancing and/or maintaining BMD in women. Thus, the purpose of this study was to use the meta-analytic approach to examine the effects of aerobic exercise on regional BMD at the lumbar spine, femur, and radius in women.

METHODS

Data Sources

Computerized literature searches of articles indexed between January 1966 and December 1998 were performed using MEDLINE, Embase, Current Contents, Sport Discus, and Dissertation Abstracts International Databases. The key words used in this literature search were "exercise" and "bone". While this broad approach to searching the literature will result in the retrieval of a greater number of articles to review, it should decrease the number of studies missed when a more narrow and focused search is conducted. In addition to computerized literature searches, the reference lists from both original and review articles were examined in order to identify any studies that had not been previously identified and that appeared to contain information that may have met our inclusion criteria. Finally, three experts on exercise and bone density (Dr. David Nichols, Dr. Charlotte Sanborn, and Dr. Christine Snow) reviewed our reference list for thoroughness and completeness.

Study Selection

The inclusion criteria for this study were as follows: (1) randomized or nonrandomized trials that included a comparative nonexercise group, (2) aerobic exercise as the only intervention, (3) adult female humans (mean study age, 18 years or older) as subjects, (4) journal articles, dissertations, and masters theses published in the English-language literature, (5) studies published and indexed between January 1966 and December 1998, (6) BMD (relative value of bone mineral per measured bone area) assessed at the femur, lumbar spine, or radius, (7) training studies lasting a minimum of 16 weeks. Only information that met the above criteria was included in our analysis. Thus, for example, if BMD was also assessed in women performing progressive resistance exercise as the primary training modality, we did not include this information since it did not meet our inclusion criteria. Because dissertations and masters theses may eventually become full-length journal articles, we cross-referenced between the two in order

to avoid duplication. We did not include abstracts and conference papers from national meetings because of the paucity of data provided as well as the inability to obtain complete data from the authors. Studies published in foreign language journals were also not included because of the potential error in the translation and interpretation of findings. Studies that met our inclusion criteria were also examined to ensure that the same subjects were not included in more than one study [8] For studies that met our inclusion criteria but did not provide appropriate information on changes in BMD, personal contact was made with the authors in an attempt to retrieve such information.

Data Abstraction

Coding sheets that could hold 242 items per study were developed and utilized in this study. In order to avoid inter-coder bias, all data were independently abstracted by both authors. The authors then met and reviewed every data point for accuracy and consistency. Disagreements were resolved by consensus. The major categories of variables coded included study characteristics, physical characteristics of subjects, and primary and secondary outcomes.

Statistical Analysis

Primary Outcomes. The primary outcomes in this study were changes in BMD at the lumbar spine, femur, and radius calculated using the standardized difference effect size (ES) approach. This was accomplished by subtracting the change outcome in the exercise group from the change outcome in the control group, and then dividing this difference by the pooled standard deviation of the exercise and control groups.[9] This measure provides one with a statistic similar to a z-score. In general, an ES of 0.20 is considered a small effect, 0.50 a moderate effect, and 0.80 a large effect.[10] An ES of 0.30 for example, means that the exercise group differed from the control group by three-tenths of a standard deviation in favor of the exercise group. Using a z-

score table, this means that the exercise group would do better than approximately 62% of the control group. We used this approach versus the original metric because of the various ways in which the authors reported data on changes in BMD and because we also wanted to maximize the number of studies and outcomes that could be included in our analysis. All ESs were then corrected for small-sample bias.[9] For those studies that did not report change outcome variances, these were estimated using previously developed methods.[11] T-distribution 95% confidence intervals were calculated for all outcomes. If the 95% confidence intervals included zero (0.00), it was concluded that there was no statistically significant effect of exercise on BMD. A random-effects model was used for all analyses.[9]

Heterogeneity of ESs was examined using the Q statistic.[9] For studies that included multiple outcomes because of more than one group, net changes were initially treated as independent data points. However, in order to examine the influence (sensitivity) of each study on the overall results, analyses were performed with each study deleted from the model for ES changes at the lumbar spine, femur, and radius. Publication bias (the tendency for journals and/or authors to publish studies that yield statistically significant results) was examined using a funnel plot.[12] This was accomplished by plotting the sample size on the vertical axis and ES changes in BMD on the horizontal axis. Usually, smaller studies will be more dispersed at the bottom of the funnel while larger studies will be more congregated at the top. A gap at the bottom of the funnel on the left side indicates that small studies yielding null or negative results may be missing. Study quality was assessed using a three-item questionnaire designed to assess bias, specifically, randomization, blinding, and withdrawals/dropouts.[13] The number of points possible ranged from a low of 0 to a high of 5. All questions were designed to elicit yes (1 point) or no (0 points) responses. The questionnaire took less than 10 minutes per study. The

questionnaire has been shown to be both valid (face validity) and reliable (researcher inter-rater agreement, r = 0.77, 95% confidence interval = 0.60 to 0.86).[13]

Subgroup Analyses. Subgroup analyses for ES changes at the lumbar spine and femur were performed using ANOVA-like procedures for meta-analysis.[9] These procedures provide statistics for both within (Q_w) and between (Q_b) group differences. A random-effects model was used for all analyses. Subgroup analyses were performed for ES changes at the lumbar spine and femur according to type of publication (journal versus dissertation), country in which the study was conducted (USA versus other), study design (randomized versus nonrandomized controlled trial), whether subjects were postmenopausal, calcium supplementation, type of BMD assessment (dual-energy x-ray absorptiometry, dual photon absorptiometry, quantitative computed tomography), and higher versus lower impact activity. Higher impact activities included exercises such as running, jumping, and aerobic dance with both feet off the ground, while lower impact activities included exercises such as walking and low-impact aerobic dance with both feet on the ground. ES changes in BMD at the femur were also examined when data were partitioned according to whether drugs were taken that could enhance BMD, cigarette smoking, diet, previous physical activity, and the specific site that BMD was assessed (femoral neck, trochanter, Ward's triangle, intertrochanteric). Insufficient data were provided to examine ES changes in BMD at the lumbar spine according to whether drugs were taken that could enhance BMD, cigarette smoking, diet, previous physical activity, and the specific site that BMD was assessed. For both the lumbar spine and femur, insufficient data were provided to examine changes in BMD when partitioned according to alcohol consumption and previous fractures. We were unable to partition the results according to training modality because of the variety of activities in which the subjects participated. We did not perform subgroup analysis for changes

in BMD at the radius because of the small sample size. In addition, we were not able to examine differences between the radius and other sites at the forearm (for example, ulna) because of insufficient data.

Regression Analysis. Potential associations between ES changes in BMD at the lumber spine and femur were conducted using simple weighted least-squares regression according to procedures developed by Hedges and Olkin.[9] Variables included study quality, percent dropout, initial BMD, age, height, initial body weight, changes in body weight, initial body mass index, changes in body mass index, initial percent fat, changes in percent fat, initial lean body mass, changes in lean body mass, initial maximum oxygen consumption ($ml/kg^{-1}/min^{-1}$), changes in maximum oxygen consumption ($ml/kg^{-1}/min^{-1}$), years past menopause, initial calcium intake, changes in calcium intake, reliability of BMD measurements, length, frequency, intensity, and duration of training, total minutes of training (length x frequency x duration), and compliance, defined as the percentage of exercise sessions attended. Insufficient data were available to examine ES changes in BMD and resting heart rate. We did not conduct regression analyses for ES changes in BMD at the radius because of the small sample size. We were unable to conduct any type of multiple regression analyses because of missing data for different sets of variables.

Secondary Outcomes. Secondary outcomes (changes in body weight, body mass index, percent body fat, lean body mass, maximum oxygen consumption, resting heart rate, calcium intake) were calculated as the difference (exercise minus control) of the changes (initial minus final) in these mean values. With the exception of the use of the original metric versus standardized difference approach, changes in secondary outcomes were examined using the same procedures as those for BMD.

An independent t-test (2-tailed) was used to compare differences in study quality between journals and dissertations. Unless otherwise noted, all results are reported as $\bar{x} \pm SD$. The alpha level for statistical significance was set at $P \leq 0.05$.

RESULTS

Study Characteristics

Twenty-seven studies met the criteria for inclusion,[14,15-40] however, we were unable to retrieve necessary data from three studies.[15,27,28] This resulted in a percent loss of approximately 11%. Thus, 24 studies representing 31 exercise and 27 control groups (some studies had more than one group) were included in our final analysis.[14,16-26,29-40] From these 24 studies, 31 effect sizes were generated for the lumbar spine, 42 for the femur, and 11 for the radius. Twenty-two of the studies were published in refereed journals[14,17-26,29,31-40] while the other two were dissertations.[16,30] Thirteen studies were conducted in the United States,[14,16,19,20,22,26,30,31,33,34,37-39] three in Australia,[18,35,36] 2 each in Finland,[24,25] Japan,[23,40] and the United Kingdom,[17,21] and 1 each in China[29] and Scotland.[32] Thirteen of the studies were randomized controlled trials[16,17,21-25,29,31,32,35,36,39] while 11 were nonrandomized controlled trials.[14,18-20,26,30,33,34,37,38,40] Study quality ranged from 0 to 5 ($\bar{x} \pm SD = 1.75 \pm 1.51$). There was no statistically significant difference in study quality between those studies published in journals and dissertations ($p = 0.65$). A total of 1,029 subjects (517 exercise, 512 control) completed pre and post assessments of BMD. The average number of subjects ranged from 5 to 49 in the exercise groups ($\bar{x} \pm SD = 17 \pm 12$) and 4 to 48 in the control groups ($\bar{x} \pm SD = 19 \pm 15$). Percent dropout, defined as the percentage of subjects that did not complete the study, ranged from 0% to 63% in the exercise groups ($\bar{x} \pm SD = 20 \pm 16\%$) and 0% to 43% in the control groups ($\bar{x} \pm SD = 10 \pm 11\%$).

Subject Characteristics

A description of the subject characteristics is shown in Table 1. Six studies reported that all of the subjects were white,[14,22,30,31,33,36] one reported that all subjects with the exception of one (a black person) were white,[20] one reported that all subjects were Chinese,[29] while another reported that all subjects were Japanese.[40] Nineteen studies reported that all subjects were postmenopausal,[14,17-23,26,29-33,35-38,40] two reported that some subjects were postmenopausal,[25,34] while three reported that none of the subjects were postmenopausal.[16,24,39] Fourteen studies reported that none of the subjects were taking any type of hormone replacement during the study, [14,17-19,23,30-36,38,40] while six reported that some of the subjects were taking some type of hormone replacement therapy.[20-22,24,25,37] One study had two separate groups of subjects in which one group took some type hormone replacement therapy while the other did not.[26] Nine studies reported that all subjects were taking some type of calcium supplementation during the study,[16,20,26,31-33,35,37,39] five reported that none of the subjects were taking any type of calcium supplementation,[19,22,23,36,40] while two reported that some of the subjects took some type of calcium supplementation.[21,30] Another study had two separate groups of subjects, one that took some type of calcium supplementation and another that did not.[29] One other study reported that all of the subjects in the control group took some type of calcium supplementation while some in the exercise group did so.[14] Eight studies reported that food intake did not change during the study[14,17,19,22,24,26,32,38] while one reported that it did.[33] Six studies reported that none of the subjects smoked cigarettes,[24-26,30,36,38] while another four reported that some of the subjects smoked.[17,19,21,37] One study reported that none of the subjects in the control group smoked but that some of the subjects in one of the two exercise groups smoked.[31] Another study reported that some of the subjects in the exercise group smoked but that none of the subjects in the control

group did.[18] Two studies reported that some subjects consumed alcohol during the study.[18,32] Two other studies reported that none of the subjects had previous fractures,[29,38] while another reported that subjects did have previous fractures.[21] Thirteen studies reported that none of the subjects had been previously active prior to taking part in the study,[14,17,20,22,24-26,30,31,33,37,38,40] while another six reported that some of the subjects had been previously active.[16,19,21,35,36,39] One study reported that none of the subjects in the control group had been previously active prior to taking part in the study but that subjects in the exercise group had been previously active.[34]

Bone Density Assessment Characteristics

Twelve studies assessed BMD at the lumbar spine using dual-energy x-ray absorptiometry (DEXA), [16,17,21,23-26,29,35,38-40] 7 studies used dual-photon absorptiometry (DPA),[14,18,20,22,30,31,34] and 2 used quantitative computed tomography (QCT).[19,32] One other study used both DPA and QCT to assess BMD at the lumber spine.[33] For those studies that reported such data, the vast majority reported the assessment of BMD at the L2-L4 sites.[16,17,20,22-25,29-31,34,38,39] Three studies reported the assessment of BMD at the L1-L4 sites,[14,35,40] one at the L1-L2 sites,[19] and another at the L1-L3 and L2-L4 sites.[33] Between-study mean reliability (coefficient of variation) of BMD assessment at the lumber spine ranged from 0.4% to 3%. Ten studies used DEXA to assess BMD at the femur,[16,17,21,24-26,29,35,38,39] while another 5 used DPA.[14,18,30,33,34] Fifteen studies reported assessment of BMD at the femoral neck,[14,16-18,21,24-26,29,30,33-35,38,39] 7 at Ward's triangle,[16,18,26,29,34,38,39] 8 at the trochanter,[16,18,24,26,34,35,38,39] and 2 at the intertrochanter.[29,35] One study reported BMD assessment at the distal femur,[24] while another reported assessment of the total femur.[35] Mean between-study reliability (coefficient of variation) for BMD assessment at the femur ranged from 0.5% to 4.4%. Eight studies reported assessment of BMD at the forearm,[24-26,30,33,34,36,37] however, we were unable to identify whether one of the studies assessed

BMD at the radius.[36] Four studies used single-photon absorptiometry (SPA) to assess BMD at the radius[30,33,34,37] while three used DEXA.[24-26] Mean between-study reliability (coefficient of variation) ranged from 0.5% to 5.0%.

Training Program Characteristics

A description of the training program characteristics is shown in Table 2. Overall, the most common activity included in these exercise interventions was walking. Specifically, five studies limited the training modality to primarily walking[17,19,21,23,33] two to jogging,[16,39] and two to a combination of walking and jogging.[31,38] Two other studies had subjects participate primarily in aerobic dance[32,34] while another two employed walking[35,36] or aerobic dance,[18,22] as well as other activities. One study limited participants' exercise to stair stepping and other miscellaneous activities,[29] while another limited exercise to stationary cycling.[14] Two other studies had participants take part in a combination of walking, jogging, cycling, stair stepping and other activities,[20,25] one had subjects perform walking, jogging, and stair stepping,[26] and another had subjects walk, swim and perform other various activities.[40] Another study had subjects perform aerobic dance, stair stepping, and other assorted activities,[24] while another had subjects perform a variety of different but unspecified activities.[37] One final study had one group of subjects that walked and another group that swam.[30]

Primary outcomes

Lumbar spine. The overall results for ES changes in lumbar spine BMD are shown in Table 3. As can be seen small, but statistically significant ES changes in lumber spine BMD were observed. These changes were equivalent to a 0.37% increase in the exercise groups and a 1.87% decrease in the control groups. No statistically significant heterogeneity was found for changes in lumbar spine BMD. Funnel plot analysis was suggestive of publication bias. With

each study deleted from the model once, ES changes in BMD ranged from a low of 0.27 ± 0.42 (95% CI = 0.12 to 0.44) to a high of 0.36 ± 0.48 (95% CI = 0.18 to 0.54).

Femur. The overall results for ES changes in BMD at the femur are shown in Table 3. As can be seen, small but statistically significant changes in BMD at the femur were observed. These changes were equivalent to a 1.37% increase in the exercise groups and a 0.58% decrease in the control groups. No statistically significant heterogeneity was found for changes in BMD at the femur. Funnel plot analysis was suggestive of publication bias. With each study deleted from the model once, ES changes in BMD at the femur ranged from a low of 0.21 ± 0.34 (95% BCI, 0.10 to 0.32) to a high of 0.26 ± 0.38 (95% BCI, 0.14 to 0.38).

Radius. The overall results for ES changes in BMD at the radius are shown in Table 3. As can be seen, changes in BMD at the radius were not statistically significant. ES changes were equivalent to a 0.08% decrease in BMD for the exercise groups and a 0.75% decrease in the control groups. No statistically significant heterogeneity was found for changes in BMD at the radius. Funnel plot analysis was not suggestive of publication bias. With each study deleted from the model once, ES changes in BMD at the radius ranged from a low of 0.02 ± 0.37 (95% BCI, -0.25 to 0.28) to a high of 0.17 ± 0.42 (95% BCI, -0.13 to 0.48).

Subgroup and Regression Analysis

Greater ES changes in BMD at the femur were observed for those subjects who received some type of calcium supplementation ($\bar{x} \pm$ SD, calcium supplementation = 0.33 ± 0.42; no calcium supplementation = -0.24 ± 0.44; $Q_b = 4.55$, $p = 0.03$). None of the other subgroup analyses at the lumber spine and femur were statistically significant or clinically important.

Secondary Outcomes

A statistically significant increase was observed for changes in maximum oxygen consumption ($\bar{x} \pm SD = 1.86 \pm 2.17$ ml/kg^{-1}min^{-1}, 95% CI = 0.31 to 3.41). No statistically significant or clinically important changes were found for any of the other secondary outcomes.

DISCUSSION

One of the primary roles of meta-analysis is to attempt to arrive at some overall conclusion(s) regarding a particular body of research. The overall results of this study suggest that aerobic exercise has a small but positive effect on BMD at the lumbar spine and femur in both premenopausal and postmenopausal women, and that this effect appears to be the result of increasing and/or preserving BMD. The fact that a similar effect was not found at the radius is not surprising given the fact that it appeared that all of the exercise interventions that the studies employed focused on loading the lower extremities. Thus, specific loading at all sites, including the radius, may be necessary in order to help increase and/or preserve BMD at that particular site. The overall results observed in this study are similar to our previous and less complete work in which comparable changes in BMD were reported.[5-7]

While the results of this study are positive with respect to changes in BMD at the lumbar spine and femur, the clinical importance of such small changes (approximately 2%) is not known, especially as it relates to fracture risk. Indeed, it may be that postmenopausal women might need other types of nonpharmacologic and pharmacologic interventions in addition to, or in lieu of, aerobic exercise in order to have a significant impact on increasing and/or preserving BMD and subsequently reducing fracture risk. For example, a recent meta-analysis reported that 10 milligrams per day of alendronate over a period of 3 years in postmenopausal osteoporotic women reduced the estimated cumulative incidence of nonvertebral fractures from 12.6% in the placebo group to 9.0% in the alendronate group.[41] This coincided with an increase in BMD of

approximately 8.8% at the spine, 7.8% at the trochanter, and 5.9% at the femoral neck.[41] Since the changes in BMD observed in this meta-analysis were much smaller, it is difficult to generalize as to how these changes impact subsequent fracture risk. It would appear plausible to suggest that future studies examining the effects of exercise on changes in BMD attempt to address the clinical importance of these changes on subsequent fracture risk.

The fact that we found greater changes in BMD at the femur for those studies that included calcium supplementation suggests that the combination of the two may be necessary in order to increase and/or preserve BMD in women. This supports previous work which found that calcium supplementation was necessary in order to maximize the benefits of exercise on BMD.[42]

We were surprised to find that both higher and lower impact activity yielded similar benefits at both the femur and lumbar spine, especially since it is generally believed that higher impact activity will have a more positive effect on BMD. However, our results support other work that reported similar BMD results for both higher and lower impact activities.[22] The former not-withstanding, our results need to be interpreted with caution since the issue of mechanical loading and skeletal integrity is still a controversial area in need of additional research.[43] Furthermore, since few studies reported the specific ground-reaction forces associated with the intervention employed, we were limited to developing a somewhat arbitrary classification system.

Despite the fact that meta-analysis is a quantitative approach for reviewing a body of literature, subjective decisions still have to be made. For example, in this investigation, we chose to include unpublished studies (dissertations) in our analysis. While the inclusion of unpublished studies in scientific overviews is controversial, we believe that if appropriate resources are available, unpublished studies should not be systematically excluded. Rather, they should be

included and examined for potential differences when compared to published work. This is especially true given the fact that there is a bias towards publishing studies that yield statistically significant and positive results. For example, Sterling et al.[44] found that approximately 96% of selected psychology journals and 85% of selected medical journals published studies that yielded a statistically significant result. The inclusion of unpublished work in scientific overviews is a feeling that is shared by the vast majority of meta-analysts and methodologists, as approximately 78% believe that unpublished material should definitely or probably be included in scientific overviews.[45] Alternatively, it may be argued that the inclusion of unpublished work is inappropriate because it has not gone through the peer review process and/or that such studies were never submitted for publication consideration because of the feeling that they may have been flawed because of some type of methodological problem. However, the fact that we found no statistically significant difference in study quality between published and unpublished work, as well as the fact that we found no difference in ES results when our data were partitioned according type of publication, resulted in us leaving this information in our analysis.

Another subjective decision we made was the inclusion of non-randomized controlled trials. We believe that it is important to include non-randomized trials at least in the exploratory phase in order to see if they differ from randomized trials. Since our subgroup analyses revealed no statistically significant differences in ES between randomized and nonrandomized trials at any of the sites assessed, we chose to include these in our final analysis.

While it appears that aerobic, site-specific exercise has a small but positive effect on BMD in adult women, these results need to be interpreted with regard to the following caveats. First, the fact that our funnel plot analysis was suggestive of publication bias for both lumbar spine and femur results may warrant caution in the interpretation of our findings. We chose to use this

quasi-statistical approach because the statistical approaches that have been developed to date are not grounded in formal statistical theory and make assumptions that are doubtful or indefensible.[46] However, it is also important to realize that the sensitivity of funnel plots for detecting publication bias has not been assessed systematically.[46] Second, the very nature of meta-analysis dictates that the meta-analysis itself inherits the limitations of the studies included in the analysis. For example, we were unable to perform subgroup analyses of ES changes in BMD at the lumbar spine according to whether drugs were taken that could enhance BMD, cigarette smoking, diet, previous physical activity habits, and the specific site at which BMD was assessed. In addition, insufficient information was available to examine ES changes in BMD at both the lumbar spine and femur according to alcohol consumption, previous fractures, and training modality. Furthermore, we were limited to conducting simple versus multiple regression analysis because of missing data. The ability to include this missing information may have yielded some interesting results. However, while missing data is a common problem in meta-analytic research, it should not preclude one from conducting a quantitative review. In fact, one of the very reasons for conducting a meta-analysis is to identify areas of weakness and provide directions for future research. With the former in mind, we believe that future studies should include, and editors publish, complete information regarding whether any drugs were taken that could enhance BMD, cigarette smoking, diet, previous physical activity habits, alcohol consumption, and previous fractures. In addition, future studies should probably assess and report the different ground-reaction forces associated with the physical activity interventions they employ. We believe that this is critical to the establishment of more precise guidelines aimed at enhancing BMD.

In conclusion, the overall results of this study suggest that aerobic exercise has a small but positive effect on BMD at the lumbar spine and femur in women.

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Table 1. Subject Characteristics

Variable	Exercise N	Exercise ($\bar{x} \pm SD$)	Control N	Control ($\bar{x} \pm SD$)
Age (years)	31	57.9 ± 12.7	27	58.2 ± 13.2
Height (cm)	22	160.7 ± 4.3	19	161.5 ± 4.4
Weight (kg)	25	64.7 ± 6.6	21	64.2 ± 6.4
BMI (kg/m^2)	24	24.9 ± 1.9	21	24.6 ± 1.9
Fat (%)	13	38.2 ± 4.8	10	37.9 ± 6.5
Lean mass (kg)	13	41.2 ± 3.5	10	39.8 ± 2.8
Initial VO_{2max} ($ml/kg^{-1}min^{-1}$)	16	23.4 ± 4.2	11	23.9 ± 5.0
Initial RHR (bpm)	4	76.7 ± 3.7	2	74.15 ± 4.5
Postmenopausal (years)	22	10.0 ± 5.4	18	11.7 ± 5.8
Calcium (mg)	19	934 ± 340	16	938 ± 344

Note: N means number of groups reporting mean data; BMI means body mass index; RHR means resting heart rate.

Table 2. Training Program Characteristics

Variable	N	$\bar{x} \pm SD$
Length (weeks)	31	53 ± 23
Frequency (days/week)	28	3 ± 1
Intensity (% VO_{2max})	7	75 ± 8
Duration (minutes/session)	22	33 ± 11
Total minutes	22	$5{,}046 \pm 3{,}159$
Compliance (%)	21	83 ± 12

Notes: N means number of groups reporting mean data; Total minutes calculated as the product of length, frequency, and duration.

Table 3. Overall results for BMD.

Variable	ES(#)	$\bar{x} \pm SD$	95% CI	Q(p)
Lumbar spine	31	0.33 ± 0.49	0.16 to 0.50*	33.65(0.29)
Femur	42	0.25 ± 0.35	0.14 to 0.35*	32.93(0.81)
Radius	10	0.10 ± 0.45	-0.20 to 0.41	9.99(0.44)

* means significantly different from zero.